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Parity and Breastfeeding among African-American Women: Differential Effects on Breast Cancer Risk by Estrogen Receptor Status in the Women's Circle of Health Study

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Abstract

Purpose—It has long been held that parity reduces risk of breast cancer. However, accumulating evidence indicates that the effects of parity, as well as breast feeding, may vary according to estrogen receptor (ER) status. We evaluated these associations in a case-control study among African-American women New York City and New Jersey.

Methods—In the Women's Circle of Health Study (WCHS), including 786 African-American women with breast cancer and 1015 controls, data on reproductive histories were collected from in-person interviews, with tumor characteristics abstracted from pathology reports. We calculated number of live births and months breastfeeding for each child, and examined each in relation to breast cancer by ER status, and for triple negative (TN) breast cancer.

Results—Although associations were not statistically significant, having children was associated with reduced risk of ER+ breast cancer (odds ratio (OR) 0.82, 95% confidence interval (CI); 0.58–1.16), but increased risk of ER - tumors, with associations most pronounced for TN breast cancer (OR=1.81, 95% CI 0.93–3.51). Breastfeeding gave no additional benefit for ER+ cancer, but reduced the risk of ER− disease associated with parity.

Conclusions—Accumulating data from a number of studies, as well as our own in African-American women, indicate that the effects of parity and breastfeeding differ by ER status. African-American women are more likely to have children and not to breastfeed, and to have ER -

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and TN breast cancer; it is possible that breastfeeding in this population could reduce risk of more aggressive breast cancers.

Keywords

breast cancer; parity; breastfeeding; African-American; estrogen-receptor negative; triple negative

Introduction

In the last several decades, a number of risk factors have been identified for breast cancer, many of which are associated with reproductive and hormonal factors (1, 2). Positive associations have been found between breast cancer and early age at menarche, nulliparity, late age at first pregnancy among parous women, late age at menopause, and use of hormone replacement therapy (HRT), with some inconsistencies in the literature in relation to breastfeeding (3). The majority of these studies, however, were conducted among white women of European ancestry (EA).

It is becoming quite clear that breast cancer is not one disease; tumor characteristics, such as expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), affect cancer prognosis (4–6). There is also increasing evidence that the *etiology* of breast cancer may also differ according to expression status of ER, PR and HER2. The identification of intrinsic tumor subtypes through gene expression arrays, later validated using immunohistochemistry (IHC) for several markers (ER, PR, HER2, CK5/6, EGFR), greatly elucidated our understanding of breast cancer heterogeneity, as well as distributions of subtypes by age and ethnic/racial backgrounds (7, 8). In the first study to investigate intrinsic breast cancer subtypes using IHC, the Carolina Breast Cancer Study (CBCS) found that ER positive (ER+) and luminal A breast cancers (positive for ER, PR and negative for HER2) were most common in EA women and older women, and ER negative (ER−) and basal-like breast cancer (negative for ER, PR, HER2 and expression of ck5/6 and EGFR) was most common among women of African ancestry (AA), particularly younger women (8).

Because ER+ and luminal A breast cancers are more common among older EA women, it is intuitive to consider that the associations with ‘known’ risk factors for breast cancer, derived from studies of mainly older EA women, may not be the same in AA women, among whom there is a greater prevalence of ER− tumors. In fact, Millikan and colleagues, using pathology data to define breast tumor subtypes in EA and AA women, showed that, while parity was associated with decreased risk of developing luminal A breast cancer, it actually *increased* risk for basal-like breast cancer (8). Furthermore, while breastfeeding added no additional reduction in risk of luminal A breast cancer, it completely reduced the increased risk associated with parity for basal-like breast cancer.

Since that seminal paper from the CBCS, a number of studies have been conducted to evaluate if parity and breastfeeding are differentially associated with risk of breast cancer according to ER, PR, and HER2 status, and the intrinsic subtypes. As reviewed in (9), the majority of studies, to date, have replicated associations whereby parity reduces risk of ER+ breast cancer, but increases risk of ER− disease. Findings regarding the effects of breastfeeding on ER status are less consistent, but appear strongest for ER− breast cancer and among AA women (reviewed in (10)). In this study, our goal was to examine associations between parity, breastfeeding and breast cancer by ER status, as well as triple negative (TN) breast cancer, among AA women. These analyses were conducted using data from the Women’s Circle of Health Study (WCHS), a case-control study of breast cancer conducted in metropolitan New York City and several counties in New Jersey.

Methods

Study population

The WCHS was specifically designed to examine the role of genetic and non-genetic factors in relation to risk of early, aggressive breast cancer in AA and EA women. The study design, enrollment criteria, and collection of biospecimens and questionnaire data have been previously described in detail (11–13). Briefly, women diagnosed with incident invasive or ductal carcinoma *in situ* breast cancer were identified using hospital-based case ascertainment in targeted hospitals with large referral patterns for AAs in four boroughs of the metropolitan New York City (NYC) area (Manhattan, Brooklyn, Bronx, and Queens) as well as population-based rapid case ascertainment in seven counties in New Jersey (NJ) through the NJ State Cancer Registry (Passaic, Bergen, Hudson, Essex, Union, Middlesex, and Mercer counties). Recruitment of cases and controls in NYC and NJ began in January 2002 and March 2006, respectively, with discontinuation of NYC recruitment in December 2008. Recruitment in NJ of AA cases and controls is ongoing. The eligibility criteria for cases included in this study were: self-identified AA, 20–75 years of age at diagnosis, no previous history of cancer other than non-melanoma skin cancer, recently diagnosed with histologically confirmed breast cancer, and English speaking. Controls without a history of any cancer diagnosis other than non-melanoma skin cancer living in the same area as cases were identified through random digit dialing of residential telephone and cell phone numbers in both NY and NJ, and were frequency matched to cases by self-reported race and 5-year age categories. AA controls were also recruited from communities in the same NJ counties as the cases through churches and health fair events, with the help of community partners and advocates. Addition of these sources of controls have previously been shown to better represent the AA population at large than RDD alone (13). Following agreement to participate and informed consent, in-person interviews were conducted to query participants on a number of potential breast cancer risk factors, including reproductive histories, and to obtain body measurements and a saliva specimen. A signed release to obtain pathology data and tumor tissue blocks was part of the informed consent process for cases, and data on hormone receptors were abstracted from pathology reports by trained study staff. This study was approved by the Institutional Review Boards at Roswell Park Cancer Institute (RPCI), the Cancer Institute of New Jersey (CINJ), Mount Sinai School of Medicine (MSSM), and the participating hospitals in NYC.

Statistical analysis

Women were considered parous if they had a live birth, and for each infant, they were asked if they breastfed and if so, for how many months. For each participant, the total number of months they breastfed was calculated by summing months of breastfeeding for each birth. History of benign breast disease (BBD) was self-reported in response to the question ‘has a doctor ever told you that you had benign breast disease, such as a non-cancerous cyst or breast lump’. Menopausal status was based upon participant responses to questionnaire data regarding menstrual and pregnancy history. Women were defined as postmenopausal if they reported that they had ceased menstruation naturally at least one year prior to reference date, or if they had both ovaries removed. The median and mean age of menopause among women reporting natural menopause was 50. Therefore, women who reported that they stopped menstruating because of a hysterectomy, but did not report removal of their ovaries, were considered premenopausal if they were <50 and postmenopausal if they were ≥50. Body mass index (BMI) was defined as weight in kilograms divided by height in meters-squared, using weight and height measurements collected by interviewers during the in-person interviews.

Descriptive statistics were generated for all variables, comparing categories across controls and cases according to ER status, using chi-square tests for categorical data. In addition to testing for significant case-control differences according to ER status, we also determined p values for case-case differences between women with ER+ and ER− tumors. For multivariable analysis, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression to examine associations between parity and breastfeeding and odds of ER+ and ER− breast tumors. In a subset of cases with complete data on ER, PR and HER2 (n=585), we also computed associations with TN breast cancer (n=131). Models were adjusted for factors associated with the exposure (parity, breastfeeding) or with risk of breast cancer in our data, and included age, site, education, age at menarche, age at menopause, history of BBD, family history of breast cancer, hormone replacement therapy (HRT) use, and country of origin. BMI was not a risk factor in our data, and was not included in final models. Analyses of associations between parity and risk by ER status were further adjusted for breastfeeding; analysis of breastfeeding was limited to parous women and additionally adjusted for number of live births. Associations were evaluated among all cases and also excluding women with DCIS from the analysis. All analyses were conducted using SAS 9.3.

Results

Characteristics of the study population are shown in Table 1, with distributions of variables of interest among controls, and cases by ER status. Higher proportions of women with ER+ tumors had DCIS than those with ER− breast cancer (20% vs. 8%), and women with ER+ breast cancer were significantly older than those in the control group (p=0.01). Controls had more years of education than cases, with the most notable differences for women with ER – breast cancer (p=0.002). Family history was more prevalent among cases than controls, for both ER+ and ER− breast cancers, and BBD was more common in women with ER+ breast cancer than in both controls (p<0.001) and women with ER− tumors (p=0.03). Controls had a younger age at menopause than women with ER− (p=0.003) or ER+ (p=0.03) disease. Although not statistically significant, women with ER− breast cancer were somewhat more likely to have two or more children (68%) than controls (61%) or women with ER+ breast cancer (61%).

Adjusted logistic regression models for associations between risk of ER+, ER− and TN breast cancers in relation to parity and breastfeeding are shown in Table 2. Although associations were not statistically significant, having one or more live births was associated with a 20% decrease in risk of ER+ breast cancer, but having at least two live births was associated with *increased* risk of ER− disease (OR=1.31, 95% CI 0.80–2.13). The OR for TN breast cancer among women with two or more births was of greater magnitude (OR=1.92, 95% CI 0.99–3.72) although the association was of borderline significance. Breastfeeding, regardless of number of months, was not associated with risk of ER+ breast cancer, but it reduced risk of ER− and TN breast cancer, although associations were not significant. When parity and breastfeeding were considered together, with women who had one child and never breast fed as the referent, having two or more children did not change risk estimates for ER+ breast cancer; breastfeeding also had no effect on risk estimates in comparison to women who never breastfed, with similar null ORs in each of the categories. Parous women who never breastfed were at increased risk of ER− breast cancer, however. Women who had two or more children and never breastfed had slightly elevated risk (OR=1.28, 95% CI 0.78–2.10), with associations strongest for TN breast cancer (OR=1.60, 95% CI, 0.84–3.03). Among women who had one child and breastfed, there was a twofold reduction in risk of TN breast cancer (OR= 0.52 (0.20–1.39), although associations were not statistically significant, and breastfeeding reduced the risk associated with having two

children to unity. Analysis of associations among only women with invasive breast cancer did not alter results (data not shown).

Discussion

In this large case-control study of breast cancer in AA women, results suggested that having children was associated with reduced risk of ER+ breast cancer, but increased risk of ER− disease. The magnitude of risk was greatest for women with TN breast cancer. Having breastfed one or more children contributed no additional reduction in risk of ER+ breast cancer, but did decrease the magnitude of increased risk associated with parity among women with ER− disease, as well as TN breast cancer. Risk estimates were not statistically significant, perhaps attributable to the fairly small sample size in stratified analysis. However, the directions of odds ratio were similar to what have been previously observed in the literature, providing more confidence in our findings.

In the past several years, a number of studies have evaluated reproductive risk factors in relation to breast cancer according to ER status and/or by breast cancer subtypes. The majority of them have found that parity reduces risk of ER+ breast cancer, with either no association or increased risk for ER− and TN breast cancer. A pooled case-case analysis of 34 studies from the Breast Cancer Association Consortium (14), mostly conducted in EA women, also showed that nulliparity was more common among women with ER+ than ER− breast cancers. While there has been growing recognition of the dual effects of parity on breast cancer according to ER status, the more recent evaluation of the contributions of breastfeeding to risk of breast cancer subtypes has important implications for public health. The preponderance of data show that the greatest effect of breastfeeding is on reduction of risk of ER− breast cancer; for the most part, it appears that having a live birth is most important for ER+ disease, with little added risk reduction with additional children or with breastfeeding (reviewed in (10)).

For years, it was hypothesized that parity reduced risk either through reduction in lifetime exposure to circulating estrogens (2) or to differentiation of breast lobules to a state less susceptible to carcinogenic exposures (15). However, the more recent findings of increases in risk of ER− breast cancer with parity are supported by research conducted by Schedin and others (16–18). In animal models and in studies with human breast tumors, it has been shown that the involution period following pregnancy results in up-regulation of immune cells and wound healing factors, creating an inflammatory state that can impact carcinogenic processes. It is possible that lactation following a birth prolongs or reduces the involution process, thus reducing risk associated with parity. This may be most relevant to ER− and TN breast cancer, which appear to more influenced by inflammatory processes, whereas ER+ tumors are likely more affected by exposure to estrogens. Estrogen dependent breast cancer risk may also be mediated by permanent changes in estrogen responsiveness that occurs as a result of high levels of estrogen exposure during pregnancy, having a lasting effect on the mammary gland, even after high estrogen levels cease (19).

The growing evidence that parity increases risk of ER− and TN breast cancer, and that breastfeeding reduces that risk, may be most relevant for AA women, who are most likely to be diagnosed with ER− or TN breast cancer, to have children at a younger age (47.4/1000 before age 19, compared to 21.8/1000 in EA), and to have more children (618.2/1000) than EA women (43.4/1000) (20). AA women are also more likely to not breastfeed (21). The WCHS is the third large study of associations between parity, breastfeeding and breast cancer in AA women, and consistent with the Black Women's Health Study (BWHS) (9) and the CBCS (8), to observe the reduction of risk of ER− and TN breast cancer associated with breastfeeding. Breastfeeding has long been recognized to have numerous benefits to

infants, as well as to their mothers following childbirth. Based on the emerging evidence from studies of breast cancer, the potential for reduced risk of often deadly forms of the disease could, with further replication, be added to the lists of benefits to mothers. The AMBER consortium, pooling four studies of breast cancer in African-American women, was formed to examine these associations in an extremely large population. Consistent findings from that pooled analysis could add further impetus to widen efforts to encourage the decision to breast feed by African-American women, and to assist all women in making such choices more feasible and acceptable in society today, particularly by providing adequate conditions and more support for women who are employed.

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Table 1

Characteristics of participants in WCHS

Characteristic	Controls N=1015 (%)	ER+ N=559 (%)	p*1*	ER− N=227 (%)	p*2*	p*3*	ER−/PR−/HER2− N=131 (%)	p*4*
Invasiveness						<.0001		
In situ		110 (20)		17 (8)			1 (0.8)	
Invasive		438 (80)		206 (92)			129 (99.2)	
Age			0.01		0.55	0.28		0.48
< 40	151 (15)	70 (13)		27 (12)			20 (15)	
40–49	281 (28)	142 (25)		70 (31)			44 (34)	
50–59	383 (38)	198 (35)		82 (36)			46 (35)	
≥ 60	200 (20)	149 (27)		48 (21)			21 (16)	
Education			0.05		<0.01	0.33		0.02
≤High School	374 (37)	246 (44)		114 (50)			64 (49)	
<College Graduate	301 (30)	149 (27)		59 (26)			39 (30)	
College graduate	212 (21)	103 (18)		36 (16)			19 (14)	
Post graduate	128 (13)	61 (11)		18 (8)			9 (7)	
Family history of breast cancer			<0.01		0.03	0.87		0.05
No	898 (88)	468 (84)		189 (83)			108 (82)	
Yes	117 (12)	91 (16)		38 (17)			23 (18)	
History of benign breast disease			<.0001		0.30	0.03		0.19
No	778 (76.7)	365 (65)		166 (73)			93 (72)	
Yes	236 (23.3)	194 (35)		60 (27)			37 (28)	
Body Mass Index			0.93		0.43	0.39		0.53
< 25	180 (18)	95 (17)		43 (19)			19 (15)	
25 – < 30	287 (28)	158 (28)		72 (32)			42 (32)	
≥ 30	548 (54)	306 (55)		112 (49)			70 (53)	
Age at menarche			0.88		0.75	0.84		0.70
< 13 years	524 (51.7)	291 (52)		120 (53)			70 (53)	
≥ 13 years	490 (48.3)	268 (48)		107 (47)			61 (47)	
Age at menopause			0.03		< 0.01	0.59		0.05
Premenopausal	493 (48.8)	259 (47)		107 (48)			69 (54)	

Characteristic	Controls N=1015 (%)	ER+ N=559 (%)	p*1*	ER− N=227 (%)	p*2*	p*3*	ER−/PR−/HER2− N=131 (%)	p*4*
< 45	70 (6.9)	31 (6)		12 (5)			6 (5)	
45–49	131 (13)	53 (10)		15 (7)			7 (5)	
≥ 50	316 (31.3)	208 (38)		91 (40)			47 (36)	
Age at first live birth[5]			0.61		0.11	0.25		0.04
< 20	332 (39.2)	178 (38)		79 (40)			45 (39)	
20–24	252 (29.8)	137 (30)		69 (35)			44 (38)	
25–29	126 (14.9)	81 (18)		31 (16)			20 (17)	
≥ 30	136 (16.1)	67 (14)		19 (10)			8 (7)	
Number of live births			0.71		0.11	0.20		0.03
0	167 (16)	96 (17)		29 (13)			14 (11)	
1	234 (23)	119 (21)		44 (19)			22 (17)	
≥ 2	614 (61)	344 (62)		154 (68)			95 (72)	
Breastfeeding[5]			0.75		0.38	0.30		0.49
Never breastfed	442 (52)	237 (51.2)		110 (56)			65 (56)	
Breastfed at least one child	406 (48)	226 (48.8)		88 (44)			52 (44)	
Number of months breastfeeding[5]			0.51		0.4745	0.8067		0.29
< 6	138 (34)	70 (32)		26 (30)			14 (27)	
≥ 6	265 (66)	151 (68)		60 (70)			38 (73)	
Country of origin			<0.01		0.03	0.22		0.04
United States	823 (81)	415 (74)		168 (74)			94 (72)	
Caribbean countries	137 (14)	110 (20)		38 (17)			25 (19)	
Other	55 (5)	34 (6)		21 (9)			12 (9)	
State			< 0.001		0.66	0.06		0.33
New York	351 (35)	148 (26)		75 (33)			51 (39)	
New Jersey	664 (65)	411 (74)		152 (67)			80 (61)	
Oral Contraceptive Use			0.07		0.08	0.64		0.72
No	426 (42.1)	209 (38)		81 (36)			53 (41)	
Yes	586 (57.9)	349 (62)		146 (64)			78 (59)	
Hormone Replacement Therapy			0.10		0.06	0.54		0.21
No	890 (88)	471 (85)		187 (83)			109 (84)	

Characteristic	Controls N=1015 (%)	ER+ N=559 (%)	p[1]	ER− N=227 (%)	p[2]	p[3]	ER−/PR−/HER2− N=131 (%)	p[4]
Yes	124 (12)	84 (15)		38 (17)			21 (16)	
Smoking Status			< 0.01		0.23	0.10		0.77
Never smoker	584 (57)	353 (63)		125 (55)			76 (58)	
Former smoker	221 (22)	127 (23)		61 (27)			31 (24)	
Current smoker	210 (21)	79 (14)		41 (18)			24 (18)	

[1] Chi-square test comparing ER+ to controls

[2] Chi-square test comparing ER− to controls

[3] Chi-square test comparing ER+ to ER−

[4] Chi-square test comparing ER−/PR−/HER2− to controls

[5] Limited to parous women

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs) associated with parity and breast feeding in relation to ER and TN status in the WCHS[1]

	Controls	ER+		ER−		ER−/PR−/HER2−	
Characteristic	**N=1015**	**N=559**	**OR (95% CI)**	**N=227**	**OR (95% CI)**	**N=131**	**OR (95% CI)**
Number of live births[2]							
0	167 (17)	96 (17)	1.0 (ref)	29 (13)	1.0 (ref)	14 (11)	1.0 (ref)
1	234 (23)	119 (21)	0.79 (0.55–1.15)	44 (19)	1.03 (0.6–1.76)	22 (17)	1.14 (0.54–2.37)
≥ 2	614 (60)	344 (62)	0.82 (0.59–1.16)	154 (68)	1.31 (0.8–2.13)	95 (72)	1.92 (0.99–3.72)
P for trend			0.93		0.19		0.03
Breastfeeding[3]							
Never	442 (52)	237 (51)	1.0 (ref)	110 (56)	1.0 (ref)	65 (56)	1.0 (ref)
Ever	406 (48)	226 (49)	1.06 (0.8–1.39)	88 (44)	0.78 (0.54–1.14)	52 (44)	0.66 (0.41–1.06)
Months breastfeeding[3]							
Never	442 (52)	237 (52)	1.0 (ref)	110 (56)	1.0 (ref)	65 (56)	1.0 (ref)
< 6	138 (16)	70 (15)	1.02 (0.72–1.47)	26 (13)	0.72 (0.43–1.21)	14 (12)	0.59 (0.3–1.15)
≥ 6	265 (31)	151 (33)	1.03 (0.75–1.41)	60 (31)	0.77 (0.5–1.18)	38 (32)	0.70 (0.41–1.19)
P for trend			0.86		0.21		0.17
Parity and lactation							
1, never	140 (16)	68 (15)	1.0 (ref)	28 (14)	1.0 (ref)	15 (13)	1.0 (ref)
≥2, never	302 (26)	169 (36)	1.03 (0.71–1.48)	82 (41)	1.28 (0.78–2.10)	50 (43)	1.60 (0.84–3.03)
1, ever	94 (11)	51 (11)	1.08 (0.67–175)	16 (7)	0.77 (0.38–1.54)	7 (6)	0.52 (0.20–1.39)
≥2, ever	312 (37)	175 (38)	1.08 (0.74–1.56)	72 (32)	1.01 (0.61–1.69)	45 (38)	1.11 (0.57–2.15)

[1] Adjusted for age, state, age at menarche, age at menopause, history of benign breast disease, family history of breast cancer, hormone replacement therapy use, education, country of origin

[2] Additionally adjusted for breastfeeding

[3] Limited to parous women and additionally adjusted for number of live births